IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Michael A. Adams *et al.* Application No.: 09/842,547 Filed: April 26, 2001 For: FORMULATIONS AND METHODS OF USING NITRIC OXIDE MIMETICS AGAINST A MALIGNANT CELL PHENOTYPE Customer No.: 20350	Confirmation No. 7618 Examiner: John D. Pak Technology Center/Art Unit: 1616 DECLARATION OF MICHAEL A. ADAMS, CHARLES H. GRAHAM, JEREMY P. W. HEATON, AND LYNNE-MARIE POSTOVIT UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We, Michael A. Adams, Charles H. Graham, Jeremy P. W. Heaton, and Lynne-Marie Postovit, declare as follows:

1. We are the named and true inventors of the subject matter disclosed and claimed in the above-referenced patent application, which claims priority to U.S. Patent Application No. 60/277,469, filed March 21, 2001 and U.S. Patent Application No. 60/199,757 ("the '757 application"), filed April 26, 2000.

2. Our invention provides, *inter alia*, methods for inhibiting a malignant cell phenotype, increasing the efficacy of an antimalignant therapeutic modality against cancer cells, and treating cancer in a subject, by administering a low dose of a nitric oxide mimetic.

3. We understand that claims 1, 3, and 4 in the present application are rejected over Umansky *et al.* (*International J. of Oncology*, 16:109-117), made available to the

public on December 23, 1999. We understand that claims 2, 5, 8, 13, 16-19, and 22 in the present application are rejected over Umansky *et al.* in view of Bonavida *et al.* (U.S. Patent Publication No. 2001/0038832), filed April 11, 2001, which claims priority to U.S. Patent Application No. 60/196,210, filed April 11, 2000, and Chemical Abstracts 129:36441.

4. Prior to December 23, 1999, we conceived of and reduced to practice the claimed invention. As evidence of our conception and reduction to practice of the claimed invention prior to December 23, 1999, we have attached hereto Exhibits B and C.

5. Exhibit B contains true copies of pages from the notebook of Nicola Matthews[1], with dates redacted therefrom, that were prepared prior to December 23, 1999. The notebook pages disclose the ability of low doses (*e.g.*, 10^{-6} M, 10^{-10} M) of the nitric oxide mimetic GTN to decrease resistance of cancer cells to adriamycin (doxorubicin). In particular, the notebook pages indicate that, prior to December 23, 1999, experiments designed to determine the effects of low dose GTN on cancer cell drug resistance were well under way. Moreover, the table and figure on page 1 clearly show that administering a low dose (*e.g.*, 10^{-6} M or 10^{-10} M) of GTN to cancer cells incubated under hypoxic conditions decreased their resistance to adriamycin (as determined by the number of colonies counted), as compared to the number of cells that survived when incubated under hypoxic conditions in the absence of GTN. As such, these experiments determined that a low dose of a nitric oxide mimetic (*e.g.*, GTN) increased the efficacy of an antimalignant therapeutic modality (*e.g.*, adriamycin) against cancer cells.

6. Exhibit C contains true copies of pages from the undergraduate thesis of Lynne-Marie Postovit, with dates redacted therefrom, that were prepared prior to December 23, 1999. The abstract of the thesis discloses the study of the effects of low levels of nitric oxide mimetics such as SNP and GTN on uPAR expression

[1] Applicants have numbered the notebook pages consecutively for the convenience of the Examiner. Nicola Matthews was working under the direction of an inventor.

and cellular invasion in immortalized human trophoblasts. In particular, treatment of the trophoblasts with low levels of SNP or GTN resulted in decreased uPAR mRNA levels and an inhibition of *in vitro* cellular invasiveness. As such, these experiments determined that a low dose of a nitric oxide mimetic (*e.g.,* SNP or GTN) was effective at inhibiting malignant cell phenotypes.

7. In view of the foregoing, we respectfully submit that Exhibits B and C unequivocally establish that the claimed invention was conceived of and reduced to practice prior to December 23, 1999.

8. We hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

9. The prior invention occurred in a NAFTA country after December 8, 1993.

Dated: Dec 18, 2003

Michael A. Adams

Dated: Jan. 6, 2004

Charles H. Graham

Dated: Jan 6, 2004

Jeremy P. W. Heaton

Dated: Jan. 7, 2003

Lynne-Marie Postovit

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